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Anatomy of Prostaglandin Signals

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of zeolite structures smaller than the crystal unit cell) by control of nucleation and growth (*9*) and then form thin films by coating and assembling them on a support. However, the smallest zeolite crystals that can be achieved by systematic optimization of hydrothermal growth rarely go below the target size of 50 nm (*10*).

An alternative approach to zeolite nanocrystals is provided from a class of materials called hierarchical zeolites, which have mainly being pursued for their uses in catalysis. They consist of nanometer-sized zeolite domains connected to each other and separated by mesopores. Hierarchical zeolites include materials derived from layered zeolites (*11*) and materials made by confined synthesis in ordered mesoporous templates (*12*) or by use of dual-templating strategies (*13*). It is conceivable that through appropriate disassembly methods, hierarchical zeolites or their precursors can be fragmented to highly crystalline zeolite particles with one or more dimensions in the 1- to 10-nm range. Thinner films enabled by the disassembled structures allow the use of more expensive materials. Ten dollars or more per milligram of zeolite could be justified for thin films in the 50-nm range and allow for the use of expensive structure-directing agents and other sacrificial templates, such as ordered mesoporous carbons and polymers.

Recently (*12*, *14*), a very precise replication scheme starting from amorphous silica spheres to form crystalline zeolite particles as small as 10 nm was demonstrated. As depicted in the figure, nanometer-sized silica spheres are first used to template mesoporous carbon with precisely sized cages that are connected to neighboring cages via smaller openings. Next, zeolite crystals nucleate and grow in these interconnected cages, forming hierarchical zeolites. These hierarchical zeolites can then be fragmented into individual particles with a size similar to that of the carbon cages (and of the silica spheres used to template them). Selective membranes can be prepared by depositing these fragments as seed crystals on a support and creating a continuous film through a second round of zeolite growth (*14*).

Technical and fundamental challenges abound. In addition to isotropic particles, other shapes, like highly anisotropic lamellae, could conceivably be made and used in novel ways to form thin films (*15*). It may also be possible to tailor hierarchical zeolites and their precursors with disassembly in mind to obtain the desirable fragments in higher yield. Effective deposition methods should be developed, and mechanical and chemical stability of such thin films should be addressed. To harvest the high flux of the thin zeolite films, high flux supports and innovative module design will be required. Flux and selectivity in these films will likely be dominated by adsorption on the external surfaces and pore entrance rate processes rather than by transport in the zeolite pores. New experimental techniques (*16*) that could address these issues are emerging and will be powerful tools in understanding and tailoring nanometer-thin zeolite membrane performance.

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CELL BIOLOGY

Anatomy of Prostaglandin Signals

An enzymatic step in prostaglandin synthesis plays a key role in neuroinflammation in the mammalian brain.

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Membrane metabolism generates many lipid signals that regulate diverse cellular processes. Although most membrane-metabolizing enzymes are specific to one lipid family, some act on a range of substrates and produce lipid signals with different bioactivities. These multisubstrate enzymes act as nodes that can change the flow of information carried by the lipid signaling network by, for example, boosting the production of one family of lipids while dampening that of another. On page 809 of this issue, Nomura *et al.* (*1*) show that the enzyme monoacylglycerol lipase (MAGL) (*2*) is a critical node within the lipid signaling network, coordinating the brain's defense mechanism to neurodegeneration. They also show that inhibiting MAGL prevents neurodegeneration and chronic neuroinflammation in a mouse model of Parkinson's disease, opening a new potential avenue for treating neurodegenerative diseases.

The brain is separated from the rest of the body by the blood-brain barrier, which insulates the central nervous system against toxins as well as peripherally circulating immune cells. It has its own specialized immune system orchestrated by microglia, a type of macrophage that constantly patrols brain parenchyma (*3*, *4*). Microglia become activated in response to pathogens and neuronal damage, rapidly changing into effector cells that initiate and control immune responses. Indeed, microglia are activated by HIV, malaria, tumors, ischemic insults, autoimmune events, and neurodegeneration. However, the phenotype of these activated cells varies depending on the pathology, from releasing toxins that harm adjacent cells, to decreasing the production of toxins and producing immune mediators that protect and repair adjacent cells (*5*).

The molecular mechanisms that determine the phenotype of activated microglia are controlled by lipid signals. For example, prostaglandins promote (*6*), whereas endocannabinoids dampen (*7*), microglia activation. Accordingly, modulating cannabinoid receptor and prostaglandin receptor activity can regulate the duration and outcome of the brain's innate immune responses. Unfortunately, the development of therapies based on synthetic receptor ligands is hampered by the compensatory desensitization or sensitization that follows long-term receptor activation or inactivation, respectively (*8*). Indeed, the intense search for therapeutic compounds targeting cannabinoid

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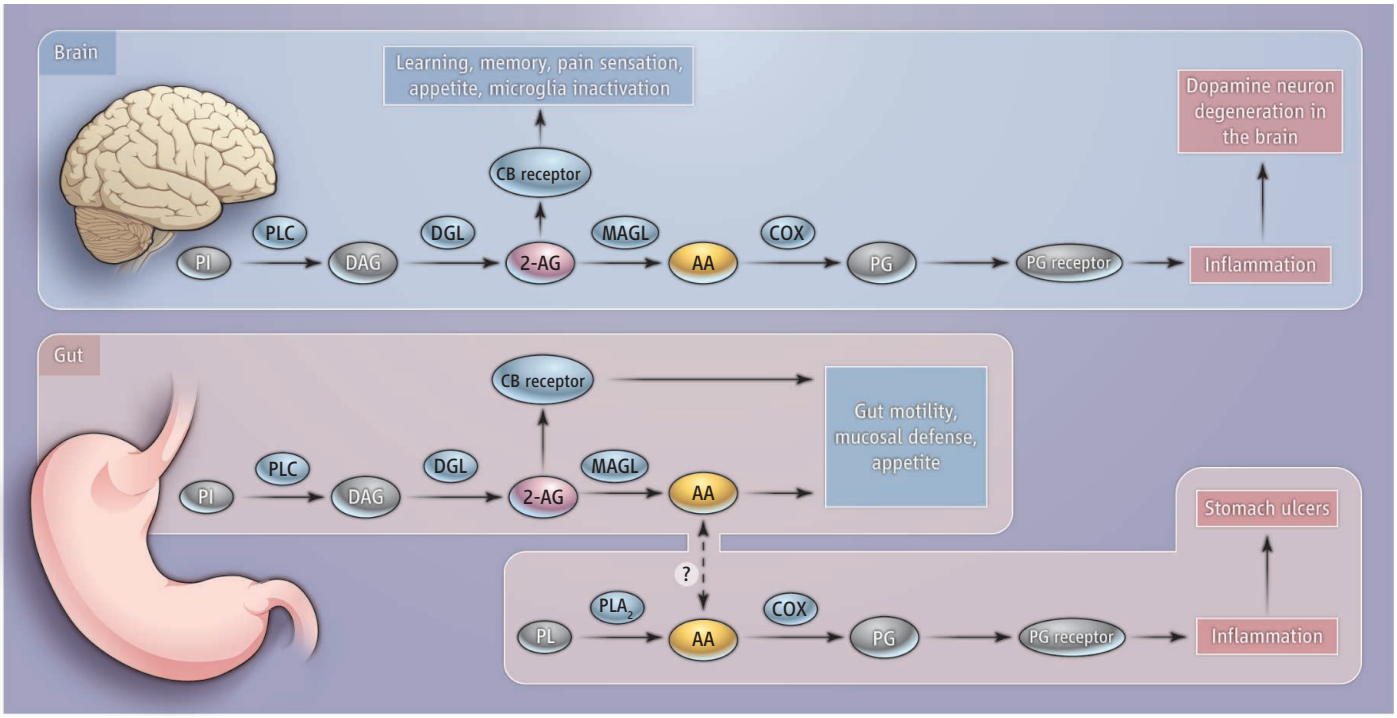

Selective pathways. (**Top**) Arachidonic acid (AA) is primarily produced by the enzyme MAGL (less is generated by PLA_2), which is then converted into proinflammatory prostaglandins (PGs) in the mouse brain. (**Bottom**) In the mouse gut, the AA is produced primarily by PLA_2. However, MAGL is also expressed in gut tissue and produces AA. PI, phosphoinositol; PL, phospholipid; PLC, phospholipase C; CB, cannabinoid; COX, cyclooxygenase; DAG, diacylglycerol; DGL, DAG, DAG lipase.

and prostaglandin receptors has yet to produce viable medicines. By contrast, cyclooxygenase 1 (COX1) and COX2 inhibitors, which block prostaglandin synthesis, are well-established treatments that benefit many patients (although a prominent toxicity is gastrointestinal bleeding). By inhibiting the enzymes that produce and inactivate lipid signals, one could control the efficacy of their signaling only where and when active endogenous signaling is already taking place. This is especially important in endocannabinoid signaling because the most abundant endocannabinoid, 2-arachidonoylglycerol (2-AG), activates multiple receptors, including cannabinoid 1 (CB1) and CB2, as well as unidentified G protein–coupled receptors that control fundamental biological processes, such as cell migration and viability (*9*). The results of Nomura *et al*. point to a new node of the lipid signaling network, MAGL, as a potential therapeutic target.

Parkinson's disease is associated with the degeneration of dopamine-containing neurons originating from the substantia nigra. The consequential chronic microglia activation and release of harmful molecules exacerbate the degeneration of these neurons (*10*, *11*). Nomura *et al*. show that in a parkinsonian mouse model, oral administration of a compound that inhibits MAGL (JZL184) boosted endocannabinoid signaling and reduced prostaglandin signaling in the brain. These actions, which dampen microglial cell activation, reduced the release of proinflammatory cytokines and prevented degeneration of dopamine-containing neurons. Although it is currently thought that phospholipase A_2 (PLA_2) is the primary enzyme for producing prostaglandins in brain, the authors show that it contributes less to prostaglandin synthesis than the MAGL pathway (see the figure). The finding therefore redefines the textbook view of prostaglandin synthesis in this particular organ.

The study of Nomura *et al*. points to a possible new avenue for developing therapeutics that target the brain's own defense mechanism against neurodegeneration. However, it is not clear why the MAGL inhibitor produced such a predominant effect in the brain, because the enzyme is also expressed by peripheral tissues. In fact, the utility of compounds that target MAGL may expand beyond treatment of chronic inflammation and degeneration. MAGL inhibitors reduce the production of fatty acid signaling lipids that mediate the migration, invasion, and survival of tumor cells, and reduce tumor growth in mouse models of cancer (*12*). However, it is important to emphasize that chronic and complete MAGL blockade by such compounds causes tolerance, impaired endocannabinoid-dependent synaptic plasticity, and desensitized brain CB1 receptors in mice (*13*). It will therefore be necessary to identify the signaling events affected by MAGL inhibitors in neurodegeneration, tumor pathogenesis, and tolerance, and determine how the drugs might benefit distinct populations of patients.

The development of unbiased analytical approaches is allowing researchers to rapidly identify how fundamental biological processes are disrupted by pathological conditions—from changes in the genetic information to profiling changes in lipid signaling and entire families of enzymatic activities. These approaches are especially powerful when coupled to classic pharmacology. The findings of Nomura *et al*. suggest that testing the preclinical therapeutic value of MAGL inhibitors could lead to the development of medicines that will benefit patients with neurodegenerative disease by heightening the brain's own protective mechanisms.

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